Does inflammation mediate the effect of pessimism on coronary heart disease? A ten-year follow-up study

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Abstract

Background

Coronary heart disease (CHD) is a notable cause of mortality worldwide. Psychosocial factors have been confirmed to have an effect on the risk for cardiovascular diseases and gradually pessimism has also been recognized as a risk factor for CHD. The mechanism by which pessimism elevates the risk for CHD is unknown. According to one theory pessimism increases low-level inflammation and an elevated inflammation level has in turn been connected with an increased risk for CHD. However, the theory of inflammation working as a mediator between pessimism and the onset of CHD has yet to be proven.

Methods

We conducted a ten-year prospective cohort study on a regional sample of three cohorts aged 52−56, 62−66, and 72−76 years at baseline (N=2,815). A revised version of the Life Orientation Test was used at baseline to define the levels of dispositional optimism and pessimism. The level of inflammation was determined by measuring the level of C-reactive protein using high sensitivity assays. These results and the data of new cases of CHD during the follow-up were used in the statistical analyses. The mediation effect of C-reactive protein between pessimism and new cases of CHD was calculated.

Results

Study subjects with a new case of CHD during the follow-up were more pessimistic and had higher C-reactive protein values at baseline than other study subjects. The pessimism score and C-reactive protein value correlated statistically significantly. We found that the connection between pessimism and developing CHD during the study period was partially mediated via the level of C-reactive protein.

Conclusion

Pessimism seemed to be a substantial risk factor for developing CHD. Pessimism was connected with the level of inflammation. The theory that elevated inflammation level mediates indirectly the connection between pessimism and the risk for CHD could be proved partially. Consequently, other mediators between pessimism and CHD remain unclear.

Background

Despite steady decreases in CHD mortality, CHD is still the cause of one in every five deaths in

Europe [1]. It is obvious that increased knowledge about the treatment, aetiology, and the

mechanisms of CHD are needed in order to improve the prevention of CHD and CHD-related

deaths.

Psychosocial factors have gradually been recognized as playing a part in the aetiology of CHD, and it has been found that psychosocial stress, depression, and pessimism, for example, are strongly connected with an elevated risk of developing CHD; furthermore, they seem to worsen the outcomes of the treatment in situations when CHD is already present [2], [3], [4], [5], [6]. However, the mechanism of this connection between psychosocial risk factors and the course of CHD is still unclear.

Inflammation plays a part in many phases of the atherosclerotic process, from endothelial dysfunction to plaque build-up [7]. There are many biomarkers indicating the inflammation process, of which C-reactive protein (CRP), when measured with high-sensitivity assays (hs-CRP), seems to be the most reliable and the most useful method [7], [8].

In our earlier studies on this population, we discovered that there is a clear connection between pessimism and CHD [4], [9]. Although some earlier studies have connected markers of inflammation with measures of optimism/pessimism, there is no previous data about the inflammation working as a possible mediator between adequately measured dispositional optimism and CHD. [10], [11], [12], [13], [14].

Hence, we conducted this ten-year follow-up study to assess whether optimism and/or pessimism affects the risk of developing CHD via inflammation. Our hypothesis was that pessimism and elevated level of inflammation are associated with each other, and this connection could mediate the effect of pessimism on developing CHD.

Methods

Study Population

Our study is a part of the GOAL (Good Ageing in Lahti region) study. The GOAL study was conducted in the region of Lahti, Finland, and its aim was to discover ways to improve the health and well-being of the local ageing population in the future. The GOAL study started in 2002 when stratified (age, sex, municipality) random samples of men and women born in

1926–30, 1936–40, and 1946–50 were drawn from the population register of all 14 municipalities in the Lahti region. A total of 4,272 subjects were invited to the study, and 2,815 (66%) of them agreed to participate. For the purposes of the present study we excluded participants with baseline CHD (N = 274). Additionally, participants were excluded due to incomplete follow-up/missing co-variate (N = 591) or death not related to CHD (N = 393) forming final study population of 1,557 subjects.

Covariate ascertainment

The study subjects were personally interviewed at the beginning of the study in 2002, and the follow-up of the study subjects lasted for ten years. At baseline in 2002, the study subjects filled in questionnaires concerning their current life status and lifestyle: the use of alcohol, smoking habits, health, possible medications, and the level of physical exercise were documented.

Study subjects were measured for height and weight, and their body mass indexes (BMI) were calculated. The blood pressure of the study subjects was measured three times and the average was documented. Venous blood samples were taken with standardized methods and blood glucose, blood total and high-density lipoprotein (HDL) cholesterol were determined. The blood samples were stored at -70 °C and the level of high sensitivity C-reactive protein (hs-CRP) for each study subject was determined in 2016 from the frozen samples.

The study subjects were asked whether they had been diagnosed with CHD by a doctor. The alcohol consumption habits were determined by using the Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) questionnaire, which is an abbreviated but as reliable as the original 10-item version of AUDIT and includes the three items on alcohol consumption [15], [16], [17], [18].

The study subjects were asked to fill in the revised version of the Life Orientation Test (LOT-R) in order to measure their dispositional optimism and pessimism, two separate measures in

the present study. LOT-R is a re-evaluated version of the Life Orientation Test (LOT), which was initially developed in the mid-1980 s to assess the effects of dispositional optimism on the self-regulation of behaviour in a wide variety of domains, some of them health-related [19]. The revision and re-evaluation was made by Scheier, Carver, and Bridges to focus its item content more closely on the subject's expectations of the future [20].

LOT-R includes four fillers and six actual statements, of which three are worded positively (e.g. 'In uncertain times, I usually expect the best') and three are worded negatively (e.g. 'If something can go wrong for me, it will'), indicating optimism and pessimism, respectively. The respondents are asked to estimate how much they agree with the statements in general on a scale of 0 ('I disagree a lot') to 4 ('I agree a lot'). A higher score refers to greater optimism or greater pessimism depending on the statement.

In this study we used separate subscale scores for the optimistically and pessimistically oriented questions. The subscales were named 'optimism' and 'pessimism', respectively.

Outcome ascertainment

At the end of the follow-up period in 2012, the study subjects were asked in the interview if they had been diagnosed with CHD by a doctor since the beginning of the study. The causes of death of those study subjects who had died during the follow-up were obtained from the statistics of The National Institute for Health and Welfare (THL).

Statistical analyses

In the statistical analyses, we used the Chi-squared test for categorical variables. To compare continuous variables, we used the nonparametric Mann−Whitney U test. Spearman´s correlation coefficient (rho) was calculated for an association between pessimism and hs-CRP at baseline. Fully adjusted logistic regression models were calculated.

In the final step, we analysed whether there were indirect mediation effects between

pessimism and new cases of CHD due to the level of hs-CRP. These effects were calculated using equations by MacKinnon and Dwyer [21], which are based on Baron and Kenny's four steps in establishing mediation [22]. The Sobel test was used to assess the statistical significance of indirect mediation effects. For analyses considering hs-CRP as a continuous variable, we performed a logarithm transformation due to the skewed distribution of hs-CRP.

Results

There were 200 new cases of CHD (69 CHD deaths and 131 cases reported in the interview by the study subjects) during the follow-up of 10 years.

Those who got CHD during the 10-year study period were at baseline older, more often men, had higher systolic blood pressure, body mass index, blood glucose and hs-CRP, smoked more often, consumed less alcohol, performed less physical exercise and were more pessimistic than the others (Tables 1 & 2). The pessimism score and C-reactive protein value correlated weakly but statistically significantly (rho 0.119, p < 0.01).

Table 1
Baseline characteristics and incidence of CHD during the 10-year follow-up period

| Risk factors at baseline (2002) | A new case of coronary heart disease during the 10-year follow up (2002–2012) | | | | Mann-Whitney U Test |
| | Yes N = 200 | | No N = 1,357 | | |
	Mean	SD	Mean	SD	p-value
Optimism score	8.45	2.05	8.39	2.07	0.69
Pessimism score	4.56	2.53	3.47	2.55	< 0.001
B-glucose (mmol/L)	6.11	1.47	5.51	0.88	< 0.001
Total cholesterol (mmol/L)	5.85	1.13	5.87	1.01	0.91
HDL cholesterol (mmol/L)	1.38	0.40	1.57	0.43	< 0.001
Age (years)	66.7	7.5	60.7	7.2	< 0.001
Systolic BP (mmHg)	150.0	19.6	143.4	17.8	< 0.001
Diastolic BP (mmHg)	85.5	10.0	86.7	9.4	0.09
Body mass index (kg/m^2)	29.2	5.1	27.4	4.4	< 0.001
Hs-CRP	3.34	6.65	2.26	3.61	< 0.001
AUDIT-C	2.55	2.43	2.81	2.23	0.025

SD = standard deviation; HDL = high density lipoprotein; BP = blood pressure; Hs-CRP = high sensitivity C-reactive protein; AUDIT-C = Alcohol Use Disorders Identification Test - Consumption

	A new case of coronary heart disease during the 10-year follow-up (2002–2012)				Chi square value	p value
	Yes N = 200		No N = 1,357			
	N	%	N	%		
Gender	123	17.2	592	82.8	23.43	< 0.001
Men (N = 715)	77	9.1	765	90.9		
Women (N = 842)						
Regular physical exercise	102	11.3	798	88.7	4.36	0.04
	98	14.9	559	85.1		
Yes (N = 900)						
No (N = 657)						
Daily smoking	101	16.9	497	83.1	14.19	< 0.001
	99	10.3	860	89.7		
Yes (N = 598)						
No (N = 959)						

Regular physical exercise = those who exercised for at least 30 minutes per session at least twice a week. Daily smoker = those who had smoked daily at least a year during their lifetime.

In the fully adjusted logistic regression (Table 3) without pessimism and hs-CRP in the model, higher age, higher blood glucose, lower HDL cholesterol, daily smoking, and lack of regular physical exercise – but not gender, systolic blood pressure, alcohol use, or body mass index – associated with the risk of developing CHD during the follow-up period (Model I). When pessimism and hs-CRP were included in the model, the result remained essentially the same (Model II). However, in this model the risk for developing CHD associated with male gender

but no more with lack of regular physical exercise. Both pessimism and higher hs-CRP associated independently with the risk of having a new case of CHD during the follow-up.

A statistically significant indirect mediation effect was found between pessimism and developing CHD via the level of hs-CRP (28.5% of the connection between pessimism and the incidence of CHD, Z = 3.03, p = 0.001) during the 10-year study period.

Table 3
Baseline characteristics and the risk of developing CHD during the 10-year follow-up.

	Model I	Model II
	OR (95% CI)	OR (95% CI)
Gender (males/females)	1.49 (0.99–2.23)	**1.59 (1.05–2.40)**
Age (years)	**1.12 (1.09–1.14)**	**1.11 (1.08–1.14)**
Systolic blood pressure (mmHg)	**1.01 (1.00-1.02)**	1.01 (0.98–1.02)
Body mass index (kg/m2)	**1.03 (1.00-1.07)**	1.02 (0.98–1.06)
B-glucose (mmol/L)	**1.29 (1.12–1.48)**	**1.28 (1.11–1.47)**
HDL cholesterol (mmol/L)	**0.51 (0.32–0.84)**	**0.53 (0.33–0.86)**
Daily smoking (yes/no)	**2.19 (1.51–3.17)**	**2.10 (1.46–3.05)**
AUDIT-C score	0.93 (0.86–1.02)	0.93 (0.85–1.01)
Regular physical exercise (yes/no)	**0.71 (0.51–0.99)**	0.74 (0.53–1.03)
Pessimism score	.....	**1.10 (1.04–1.17)**
High-sensitivity CRP (ln transformation)	.....	**1.20 (1.01–1.41)**

Fully adjusted logistic regression models: Model I is without pessimism score and hs-CRP in the model. Model II includes pessimism score and hs-CRP in the model.

Discussion

The main finding of this study was that higher level of pessimism predicted the incidence of CHD after adjusting to other predictors of CHD. Significant proportion of this effect was mediated by increased inflammation among those with more pessimism.

We are reporting for the first time the possible mediator effect of hs-CRP in the context of pessimism and cardiovascular risk. Pessimism was an independent predictor of higher incidence of CHD in both models applied. This finding is in line with a large body of evidence connecting pessimism and higher incidence of CHD [4], [23], [24], [25], [26]. Hs-CRP, a marker of inflammation, and a known predictor of cardiovascular disease, was also connected to incidence of CHD in the present population. According to our analysis hs-CRP mediated nearly 30% of the pessimism related effect on CHD.

Positive affective states have been connected with lower hs-CRP levels [27] while increasing severity of depression seems to correlate with an elevated hs-CRP level [28], [29]. In a research derived from the Heart and Soul Study, the connections between depression and inflammation, between depression and CHD, and between inflammation and CHD were affirmed. Contrary to our positive findings about the inflammation mediating the effect of psychosocial risk factor on the incidence of CHD, investigators of Heart and Soul Study found no evidence of inflammation operating as a mediator between depression and CHD [30]. Parallel findings have also been made about optimism. A study about the optimistic perception of one's CVD risk found lower rates of adverse effects of CVD among those with more optimism but this connection could not be explained by the mediating effect of the level of inflammation [31]. In that study, optimism was measured by asking the test subjects what they think about their risk of developing CHD, so the question evaluated self-rated health rather than optimism.

Even if both LOT and LOT-R were thought to be unidimensional scales (i.e. the result of the test was given as a combination of the answers to the pessimistically and optimistically oriented statements), later studies have suggested that they may have two separate independent dimensions, namely optimism and pessimism. Dividing the optimism scaling from pessimism and examining the results separately seems to lead to better prediction of

outcomes [32], [33]. In a bipolar univariate model, optimism and pessimism may hide some of each other's results. It has also been suggested that dispositional optimism could be a unidimensional continuum, but LOT-R divides it into two independent subscales, optimism and pessimism [34] and the questions worded negatively might be better at measuring this personal trait than the optimistically oriented questions. According to this theory the questions worded positively may not give consistent results, leading to the weak statistical power of the optimism subscale [13].

In our earlier study we demonstrated that in this study group, optimism and pessimism seem to be separate variables [4], a finding that has also been made in many other study groups [35], [36], [37]. In the present study, the two-factor model of optimism and pessimism – i.e. optimism and pessimism being two separate and independent variables instead of one bipolar factor – was confirmed. While the connection between pessimism and CHD appeared to be solid, optimism did not associate with the incidence of CHD.

Optimism and pessimism characterize an individual in ordinary situations. Like other personality traits, their development appears to be influenced by both heritage and environment [38], [39]. Unlike mood, for example, they seem to be stable once they have evolved, and they remain the same in different situations and over time, regardless of the negative or positive incidents [40], [41].

The association between psychosocial factors and CHD seems to be quite confident, and our study endorses the need to continue the research in this area. Our hypothesis of inflammation mediating the connection between pessimism and CHD was confirmed to a marked degree. Finding the other mediating factors between pessimism and CHD could help in understanding CHD, its aetiology and mechanism, which in turn could help in preventing and treating CHD.

The strength of our study is in its design. The study group can be seen as comprehensive one.

Ten years is a relatively long time, and the prospective nature of the study makes the results more reliable. The use of a well-known test pattern (LOT-R) in determining optimism and

pessimism makes our study more convincing. Separating optimism from pessimism seemed to clarify our results. CRP has a long plasma half-life and relative stability as a frozen sample, which makes it quite easy and reliable to measure [42].

There are a few shortcomings in this study. One of them is that we could use only self-reports for some variables, which can lead to biased information. Self-reports were used in the variables concerning life habits (e.g. smoking and the use of alcohol). However, it has been demonstrated that alcohol consumption can be estimated quite accurately using self-reports [43], [44], [45], [46] and while self-reports concerning smoking status are usually not so reliable, they are very useful when the respondents are elderly [47], like the participants in our study. We had access to the Records of Causes of Deaths, and thus we could determine the number of people who died due to CHD, but the prevalence of CHD at the beginning of the study and the number of new cases of CHD during the follow-up among those who were alive at the end of the study were based on self-reports. However, self-reports are quite reliable like earlier mentioned, and the numbers concerning CHD received by self-reports are quite similar to the prevalence and incidence rates of CHD that can be calculated from the official statistics for the same-aged population in Finland [48], [49].

It is also expected that there were some people with new CHD among those who died during the follow-up due to some other reason than CHD, and those individuals could not be included in the study. It also seems that poorly functioning and institutionalized persons had a lower participation rate than community-dwelling subjects, which can have an effect on the results [50]. In addition, the level of CRP may have been high for temporary reasons in some cases, which might have lightened our finding. Another possible form of bias is related to the fact that the levels of hs-CRP were analysed in samples that had been frozen for more than 10 years.

Consequently, there is a risk that the absolute levels of hs-CRP could have been affected by having been taken from frozen – rather than fresh – samples. However, it has been found that

CRP is relatively stable as a frozen sample [42] and the freezing time was the same for all

samples.

Conclusion

It seems that the previously identified connection between pessimism and the risk of developing CHD is partially mediated indirectly through the low-grade tissue inflammation as

we hypothesized. While the finding is significant, it means that there also are other biological

mediators between pessimism and the risk coronary heart disease.

Declarations

Abbreviations

CHD, coronary heart disease; CRP, C-reactive protein; hs-CRP, high-sensitivity C-reactive

protein; GOAL, Good Ageing in Lahti region study; BMI, body mass index; HDL, high-density

lipoprotein; AUDIT-C, Alcohol Use Disorders Identification Test – Consumption; LOT, Life Orientation Test; LOT-R Life Orientation Test re-evaluated; THL, The National Institute for Health and Welfare.

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